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(54) **Bioadhesive extruded film for intra-oral drug delivery and process.**

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Description

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a controlled-releasing medicament-containing preparation for intra-oral use. In particular it is more especially concerned with such a preparation (and the process of using it) in the form of a very thin extruded thermoplastic film (which can be in single layer or laminated multi-layer form) having at least one bioadhesive layer containing 22.4-68.3% by weight of a specified thermoplastic cellulose ether and 23.75-60% by weight of a specified homopolymer of ethylene oxide which can adhere to the mucosa of the oral cavity. The extruded film drug delivery system of the present invention, which has incorporated therein the medicament to be dispensed, is so thin and flexible when wet as to be unobtrusive to the patient after it has been properly positioned and placed in the mouth.

Description of the Prior Art

Several systems have previously been described which pertain to the delivery of drugs into the oral cavity. These include:

1. Treatment of periodontal disease with tetracycline. chlorhexidine or metronidazole loaded into hollow cellulose acetate fibers. These fibers are packed in the periodontal pockets and provide controlled release of the drug to the infected area.
2. Cast films containing ethyl cellulose/propylene glycol with chlorhexidine or metronidazole for treatment of periodontal disease.
3. An orthodontic appliance with a hydroxyethyl methacrylate/methyl methacrylate copolymer (HEMA/MMA) matrix. Sodium fluoride is incorporated into the HEMA/MMA matrix to provide sustained fluoride release and enhanced anticaries activity. HEMA/MMA with fluoride may also be attached to the tooth in the form of a wafer-like tablet.
4. Silicone/ethyl cellulose/polyethylene glycol films containing sodium fluoride are applied as coatings on orthodontic bands or in chewing gum. Controlled release of fluoride and anticaries activity is claimed.

The above systems are discussed in the "The Compendium of Continuing Education" Vol VI, No. 1, Jan.1985 p. 27-36 review article "Controlled Drug Delivery: A New Means of Treatment of Dental Disease", by J. Max Goodson, D.D.S., Ph.D. of the Forsyth Dental Center. Other systems, described in GB patent application 2,042,888 and U.S. Patents 4,292,299/4,226,848 (Teijin Ltd., Japan), use combinations of cellulosic and polyacrylate polymers. The preferred materials are hydroxypropyl cellulose ("Klucel") and a copolymer of acrylic acid ("Carbopol") that is administered in the form of thin tablets (discs), granules or powder. Other polymers that might be added are vinyl copolymers, polysaccharides, gelatin and collagen. U.S. patent 4,517,173 (Nippon Soda Co. Ltd, Japan) uses various celluloses in a multi-layered non-extruded cast film preparation.

Examples of prior art products currently on the market include ointments such as ORABASE® with Benzocaine (Squibb), Kenalog® (Triamcinolone Acetonide) in ORABASE® (Squibb) and Mycostatin® (Nystatin) ointment (Squibb).

The prior art products and delivery systems described above are useful but have the following disadvantages:

Tablets, appliances, hollow fibers are "bulky" in the mouth, are difficult to keep in place and inconvenient to apply.

Ethyl cellulose and/or silicone films do not adhere to mucosal tissue.

Ointments (i.e., ORABASE®) have an unpleasant feel and do not last very long.

Except for ORABASE®, all the foregoing systems require professional application to the tooth or periodontal pockets.

The bioadhesive film of the present invention alleviates many of the above problems. It may be applied easily by the consumer. It has very little or no mouthfeel, it has good adhesion to the mucosal tissues, and provides controlled release of the medicament.

Also EP-A-0 063 604 discloses a mucous membrane-adhering film preparation in which the one surface of water-soluble high polymer film containing pharmaceutical agents is treated to be made difficultly water-soluble. JP-A-5 890 507 discloses a film formed by an injection moulding machine or an extrusion moulding machine, the film comprising a mixture of a water-soluble polymer (water-soluble cellulose derivative), an active component (drug absorbable through the mucous membrane) arbitrary additives (diluent, taste or

scent improvers, colorants etc) and a plasticizer (polyethylene glycol).

Object of the Invention

It is an object of this invention to provide an extruded film that is an effective and convenient intra-oral drug delivery system and method for applying and delivering controlled dosages of therapeutic agents into the oral cavity. This technology may also be extended for controlled drug delivery in skin care, gynecological applications, wound care and like uses.

Summary of the Invention

The invention involves a pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multi-layered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of hydroxypropyl cellulose of molecular weight above 100,000 23.75-60% of a homopolymer of ethylene oxide of molecular weight above 100,000, 0-12.5%, of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, Carboxy methyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

The present invention is directed to an extruded single or multi-layered laminated thin (1-10 mils or 0.025-0.25 mm) film, composed of selected water soluble and/or insoluble polymers. Various therapeutic agents are incorporated into the film during manufacture which are useful for treatment of oral disorders (i.e., denture discomfort, caries, periodontal disease, aphthous ulcers, etc.).

The extruded film of the present invention must have at least one bioadhesive layer, but may also have a reservoir layer and/or an outer protective barrier membrane layer. The therapeutic agent may be incorporated into any or all of the layers. When properly formulated and fabricated, these films will adhere to wet mucosal surfaces, provide a protective barrier for injured tissue and deliver controlled/sustained dosages of medication to the infected areas. The film may be designed for localized drug delivery (i.e., the periodontal pocket, an aphthous lesion), or may allow diffusion of the drug into the oral cavity.

An example of a non-localized system would be the delivery of sodium fluoride for caries prevention. A single or laminated film with good adhesion to the tooth or mucosal tissue may be employed in which the fluoride release rates may be controlled by varying film solubilities and/or concentration of fluoride in a multi-layered film.

An example of a localized application of medication would be in the treatment of aphthous lesions. A laminated two layer film with benzocaine incorporated into the adhesive layer would directly contact the injured mucosa. The outer layer would consist of non-soluble/non-adhesive polymers that provide durability, protection and directs the delivery of benzocaine toward the lesion.

The film forming polymers that are useful in this invention are selected from pharmaceutical grade materials, or those that are considered generally regarded as safe (GRAS) as food additives. They include, hydroxypropyl cellulose, and polyethylene oxide homopolymers. Small amounts of other polymers. e.g., polyvinyl ether-maleic acid copolymers and the like may be used in small amounts as well, replacing a small portion of the other polymers. The above materials are either water soluble or swellable and are most useful in the bioadhesive layer of the film. Various non-soluble polymers may also be incorporated for modification of the film's permeability properties, such as ethyl cellulose, propyl cellulose, polyethylene, polypropylene and carboxymethylcellulose (free acid) in an amount of up to 12.5% by weight. By varying the ratios of the above polymers both the solubility and the adhesive properties of each layer of film may be controlled. Therefore, depending on the desired delivery rate, the type of disorder to be treated, the area to be treated and the medication being administered it is possible to custom design the film by selecting and blending various polymers. The final film product may also be fabricated into flexible tapes of varied thickness and width, "spots" of different sizes and shapes or other pre-shaped forms.

The medicaments and pharmaceutical agents set forth in the prior art discussed above may generally be delivered by the drug delivery system of the present invention. Usable medicaments are those which are capable of withstanding the heats and pressures generated in the extrusion process involved in making the film of the present invention. Preferred medicaments include:

Anesthetics/Analgesics - benzocaine, dyclonine HCl, phenol, aspirin, phenacetin, acetaminophen, potassium nitrate, etc.

Anticaries Agents - sodium fluoride, sodium monofluorophosphate, stannous fluoride, etc.

Anti-inflammatories - hydrocortisone acetate, triamcinolone acetonide, dipotassium, glycyrrhizinate, etc.
Antihistamines - chlorpheniramine maleate, ephedrine HCL, diphenhydramine HCL, etc.
Antibiotics - i.e., tetracycline, doxycycline hyclate, meclocycline, minocycline, etc.
Antibacterials - chlorhexidine, cetyl pyridinium chloride, benzethonium chloride, dequalinium chloride, silver sulfadiazene, phenol, thymol, hexedine, hexetidine, alexidine, etc.
Fungistats - nystatin, miconazole, ketoconazole, etc.

The above are illustrative examples of therapeutic agents that are used to treat oral disorders. The present invention is not to be limited to these specific materials especially where it is intended to deliver drug outside of the oral cavity e.g. to skin where other drugs may be desirable.

The film of the present invention has the advantage of being an extruded film, rather than a cast film. When a multi-layered film is involved, the different layers can be coextruded and then laminated together, or else each layer can be separately extruded one on the other, and then laminated together, so that the final multi-layered film is still very thin. The films of the present invention can be made in thicknesses of only 1-10 mils or 0.025-0.25 mm. The films are so thin that when placed in the mouth after they become wet they soon become unobtrusive, and hardly noticeable by most patients.

The film must always have a bioadhesive layer, which enables it to adhere to wet mucosal surfaces. The bioadhesive layer has 22.4-68.3 wt % of hydroxpropyl cellulose, 23.75-60 wt % of a homopolymer of ethylene oxide and 2.85-5 wt % of a glycol plasticizer (all percents are % by weight).

The Hydroxypropyl cellulose (HPC), useful for purposes of the present invention is commercially available from Hercules, Inc. (Wilmington, DE) under the tradename KLUCEL®. Preferred grades include Klucel MF, with a molecular weight around 600,000 and having a viscosity of 4,000-6,000 cps (Brookfield) in 2 percent water solutions, or Klucel HP, having a molecular weight around 1,000,000 and viscosity of 1500-2500 cps in 1 percent water solution. Any HPC having a Molecular Weight above about 100,000 is useful for purposes of this invention.

The homopolymer of ethylene oxide useful for purposes of the present invention has a relatively high molecular weight, i.e., above 100,000 and preferably above 3,000,000. Such polymers are commercially available from various sources. The Union Carbide Corporation material, "Polyox WSR-301", which has a molecular weight of approximately 4,000,000 - 5,000,000 is most preferred for purposes of the present invention.

The "plasticizer" useful for purposes of the present invention are selected from glycols such as propylene glycol and polyethylene glycol; polyhydric alcohols such as glycerin and sorbitol; glycerol esters such as glycerol triacetate; fatty acid triglycerides such as NEOBEE® M-5 and MYVEROLS®; mineral oil; vegetable oils such as castor oil, etc.

For the uses for the present invention contemplated here, the plasticizer should be non-toxic. The purpose of the plasticizer is to improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product.

The preferred plasticizer for use in the present invention is either propylene glycol or polyethylene glycol (such as is available from Union Carbide Corporation as their series of Carbowaxes which runs from 200 to 600 molecular weight, of which we prefer to use Carbowax 400, which has a molecular weight of 400, average.

In addition to the polymers and plasticizer which are required ingredients of the films of the present invention, minor amounts of other non-essential but customary ingredients will often be used if desired, e.g., antioxidants, preservatives, flavors, colorants.

Detailed Description

The following examples will serve to illustrate the present invention in greater detail. The units shown in the examples are parts by weight. The thickness of the layers is expressed in either mils (.001 inches) or millimeters. For easy conversion, 4 mils is approximately equal to 0.1 mm.

EXAMPLE 1 - TRIPLE LAYERED LAMINATE CONTAINING SODIUM FLUORIDE FOR ANTICARIES PROTECTION:

This three layered film laminate is comprised of a "bioadhesive" layer, a sodium fluoride "reservoir" layer and, an "outer protective barrier membrane" layer, in which the composition and thickness of each layer are as shown below:

Ingredients	Bioadhesive Layer (4 mils) (0.1 mm)	% w/w Reservoir Layer (1 mil) (0.025 mm)	Outer Protective Barrier Membrane Layer (1 mil) (0.025 mm)
Polyethylene oxide homopolymer (Union Carbide-Polyox* WSR-301)	60.0	-	-
Hydroxypropyl Cellulose (Hercules, Inc.-Klucel* MF)	30.0	20.0	24.0
Polyethylene (Allied Chemical-6A) (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol 400 (Union Carbide)	2.0	-	-
Ethyl Cellulose (Hercules, Inc.-N100F)	-	59.0	69.6
Caprylic/Capric Triglyceride (PVO Incorporated-Neobee M-5)	-	5.0	6.0
Sodium Fluoride, U.S.P.	-	16.0	0.4
	100.0	100.0	100.0

The process used to make the above laminate was :

a) Powder Blending - Each layer is made separately and all ingredients used therein except propylene glycol and Neobee M-5 (liquid plasticizers) are placed in a Patterson Kelley (PK) V-blender equipped with liquid addition capabilities. The ingredients which are all powders are blended for approximately 10-15 minutes while the liquid plasticizer is slowly added to the mix. Three separate powder blends are made, one for each layer.

b) Extrusion Process - A standard Johnson 2-1/2 inch (0,0635 m) vinyl/polyolefin extruder equipped with a single three stage screw was used to extrude the "powder blend". The temperature conditions for the water soluble powders are however quite different from those used for vinyls and polyolefins. The

temperature (°C) profile for the "reservoir" and "membrane layers" of the triple laminate was as follows:

Barrel Zone 1	100
Barrel Zone 2	125
Barrel Zone 3	135
Barrel Zone 4	145
Barrel Zone 5	160
Barrel Zone 6	170
Adapter -	180
Die Zone 1	180
Die Zone 2	180
Die Zone 3	180

The films which had a width of 18 inches (0,45 m), were extruded at approximately 20 feet/minute (6 m/min) through a flat lipped die. The temperature profile for the "bioadhesive layer" was:

Barrel Zone 1	125
Barrel Zone 2	140
Barrel Zone 3	165
Barrel Zone 4	170
Barrel Zone 5	185
Barrel Zone 6	185
Adapter -	185
Die Zone 1	185
Die Zone 2	185
Die Zone 3	185

Each layer is extruded separately with the first layer extruded as a "free film". Successive layers are extruded onto each other and laminated by passing them through heated stainless steel rollers.

Test Results:

In vitro fluoride ion release studies were conducted on samples of the above described triple laminate film measuring 0.5 cm x 1.25cm (0.625 cm^2) according to the following procedures:
The test sample is adhered to a glass slide by prewetting the film and placing the bioadhesive layer on the glass surface. The slide is then immersed in a beaker containing 100 ml of distilled water with continuous stirring. Five milliliter aliquots are withdrawn from the solution, at prescribed time intervals, and analyzed for fluoride content with an Orion Ionanlyzer equipped with a fluoride specific electrode. Release rates are then calculated from the data.

The results obtained indicated fluoride release rates in the order of 0.05-0.2 mgs/cm^2/hr for 24 hours. This falls within the desirable range for maintaining constant low levels of fluoride in the mouth and enhanced anticaries activity. Release rates may be tailored to desired use levels by modification of the film composition and construction.

EXAMPLE 2 - SINGLE LAYER ADHESIVE FILM CONTAINING HYDROCORTISON ACETATE (0.5%) AS AN ANTI-INFLAMMATORY AGENT:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox* WSR-301)	59.4
Hydroxypropyl Cellulose (Klucel* MF)	30.0
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
Butylated Hydroxy Toluene (BHT) FCC (preservative)	0.1
Hydrocortisone Acetate	0.5
	100.0

The powder blending process and extruder conditions used were the same as those described in Example I for the "bioadhesive layer" of the sodium fluoride trilaminate. In vitro tests were performed on the above film and demonstrated a prolonged drug release pattern.

EXAMPLE 3 - SINGLE LAYER ADHESIVE FILM CONTAINING TRIAMCINOLONE ACETONIDE (0.1%) AS AN ANTI-INFLAMMATORY:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox WSR-301)	59.9
Hydroxypropyl Cellulose (Klucel MF)	29.9
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
BHT	0.1
Triamcinolone Acetonide	0.1
	100.0

The powder blending process and extruder conditions used to make the film of this Example 3 were the same as those of the "bioadhesive layer" of Example I.

Other desired active medicament ingredients may be incorporated into the adhesive films of any of Examples 1-3 in place of the particular medicament used in said examples. These include Benzocaine (analgesic), Potassium nitrate (analgesic), Silver sulfadiazene (antimicrobial).

Chlorhexidine (antimicrobial), miconazole nitrate (antifungal), Benzethonium chloride (antimicrobial), Tetracycline (antibiotic) and other similar therapeutic compounds.

EXAMPLE 4 - ANALGESIC FILMS WITH POTASSIUM NITRATE

This example shows 5 variations of the film having different solubilities, resulting in different release rates.

Ingredients	% w/w 1	2	3	4	5
Polyethylene oxide homopolymer (Polyox* WSR-301)	23.75	57.00	55.00	55.00	57.00
Hydroxypropyl Cellulose, N.F. (Klucel* HF)	68.30	-	-	-	-
Hydroxypropyl Cellulose, N.F. (Klucel* MF)	-	28.40	29.90	22.40	22.40
Ethyl Cellulose	-	4.75	5.00	12.50	12.50
Polyethylene Glycol 400	1.90	1.90	2.00	2.00	2.00
Polyethylene Glycol 8000	0.95	-	-	-	-
Propylene Glycol, U.S.P.	-	2.85	3.00	3.00	3.00
BHT, F.C.C.	0.10	0.10	0.10	0.10	0.10
Potassium Nitrate, F.C.C.	5.00	5.00	5.00	5.00	3.00

The above ingredients are blended in a Patterson-Kelly powder blender equipped with liquid addition capabilities. The resulting powder blend is then extruded into film on a Killion or Johnson vinyl extruder using processing procedures similar to those of the bioadhesive layer of Example I.

EXAMPLE 5 - ANESTHETIC FILMS WITH BENZOCAINE (LAMINATE)

This is an example of a two-layer laminate. The processing conditions used were similar to those of the bioadhesive layer and outer protective barrier membrane layer of Example I.

A.	**Inner medicated bioadhesive layer**	
	Polyoxyethylene Homopolymer (Polyox* WSR-301)	57.00
	Hydroxypropyl Cellulose, N.F. (Klucel* MF)	28.40
	Polyethylene (AC-6A)	4.75
	Propylene Glycol, U.S.P.	2.85
	Polyethylene Glycol 400	1.90
	BHT, F.C.C.	0.10
	Benzocaine, U.S.P.	5.00
		100.00
B.	**Outer protective/barrier layer**	
	Hydroxypropyl Cellulose (Klucel* MF)	78.00
	Ethyl Cellulose	20.00
	Polyethylene Glycol 400	2.00
		100.00

Part A was extruded on a Johnson extruder followed by subsequent extrusion and lamination of Part B to A.

Samples were applied to oral lesions, and provided profound anesthetic effects (lasting several hours) within minutes of application.

The identical two-layer laminate may also be made by coextruding the inner medicated bioadhesive layer (Part A) and the outer protective barrier layer (Part B) through separate die slots within a coextruder and laminating the two layers together.

EXAMPLE 6 - ANESTHETIC FILMS WITH PHENOL AND DYCLONINE HCl

Four variations of a single layer bioadhesive film were made as shown below:

Ingredients	1	2	3	4
Polyethylene oxide homopolymer (Polyox* WSR-301)	59.10	54.00	59.70	58.20
Hydroxypropyl Cellulose (Klucel HF)	29.45	26.91	29.75	29.00
Ethyl Cellulose	4.93	4.50	4.98	4.85
Propylene Glycol, U.S.P.	2.96	2.70	2.99	2.91
Polyethylene Glycol 400	1.97	1.80	1.99	1.94
BHT, F.C.C.	0.09	0.09	0.09	0.10
Phenol, U.S.P.	1.50	-	-	-
Dyclonine HCl	-	10.00	0.50	3.00

Following the procedures for the bioadhesive layer of Example I, the powders were blended in P-K blender equipped with liquid addition capabilities. Resulting powders were extruded on a Killion laboratory-sized extruder.

EXAMPLE 7 - SILVER SULFADIAZENE FILMS - ANTIMICROBIAL

Three different single-layered bioadhesive films containing 1.0% 0.5% and 0.5% respectively of silver sulfadiazene (SSD) were prepared on a heated Carver laboratory press (designed to simulate extruded conditions) as shown below.

Ingredients	% w/w A	% w/w B
Polyethylene oxide homopolymer (Polyox* WSR-301)	60.00	60.00
Hydroxypropyl Cellulose (Klucel* HF)	28.9	29.4
Polyethylene (AC-6A)	5.0	5.0
Propylene Glycol, U.S.P.	3.0	3.0
Polyethylene Glycol 400	2.0	2.0
BHT, F.C.C.	0.1	0.1
Silver Sulfadiazine	1.0	0.5
	100.0	100.0

Effects on wound repair and activity against Staphylococcus aureus were evaluated in the guinea pig model. Full-thickness excisions were inoculated with 3.8×10^5 organisms, (Staph. aureus) and wound surface microbiology samples taken 10 minutes and 24 hours after treatment. Test films were placed on the wound and covered with BIOCLUSIVE® Transparent Dressings secured with elastic tape. Wound contraction was measured over an eight-day period using OPTOMAX® Computer-Assisted Image Analysis. The three films tested were the following:

A. 1.0% Silver Sulfadiazene, 125 • C/2 minutes/4 tons
B. 0.5% Silver Sulfadiazene, 125 • C/2 minutes/4 tons
C. 0.5% Silver Sulfadiazene, 150 • C/3 minutes/4 tons

SILVADENE Cream and un untreated occluded control. The results indicated that:

1. SILVADENE® treated wounds significantly inhibited full-thickness wound contraction.
2. Film A, B and C inhibited wound contraction relative to that of BIOCLUSIVE® dressed wounds.
3. The three SSD films each permitted substantially faster wound contraction than that of wounds treated daily with SILVADENE® cream.
4. All films were very active against S. aureus 24 hours after inoculation.

The films may be scaled up by using an extruder. This example demonstrates the feasibility of such a film to perform its intended purpose. Use of a press for larger samples would result in a non-uniform and lower-quality film than an extruded film.

Based on the above findings, the films were very effective antibacterial agents, while mildly inhibiting wound contraction. They offer clinicians a convenient and more effective delivery system for antimicrobials which can be place in wounds beneath any dressing or can be laminated to any acceptable dressing face.

Claims

1. A pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multilayered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of a hydroxypropyl cellulose having a molecular weight above 100,000, 23.75-60% by weight of a homopolymer of ethylene oxide having a molecular weight above 100,000, 0-12.5% by weight of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, carboxymethyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

2. The extruded film of claim 1, made in a form which is so thin and flexible when wet as to be unobtrusive to the patient when properly positioned and placed in the patient's mouth.

3. The extruded film of claim 2 having a thickness no greater than 0.25 millimeters.

4. The extruded film of claim 3 wherein, in the bioadhesive layer the homopolymer of ethylene oxide has a molecular weight from 3,000,000 to 5,000,000.

5. The extruded film of Claim 3, in multi-layer laminated form, which in addition to the bioadhesive layer also contains a reservoir layer in which at least a major portion of the medicament is contained.

6. The extruded multi-layer film of Claim 5 in which the reservoir layer consists essentially of a polymer matrix comprised of both a water soluble or swellable polymer and a non-water soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and also hydroxypropyl cellulose.

7. The extruded film of Claim 4 in multi-layer laminated form, which in addition to the bioadhesive layer also contains an outer protective-barrier membrane layer.

8. The extruded multi-layer film of Claim 7 in which the outer protective-barrier membrane layer is thinner than the bioadhesive layer, and said outer protective barrier layer consists essentially of a polymer matrix of a major proportion of a non-water-soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and a minor proportion of hydroxypropyl cellulose.

9. The extruded multi-layer film of Claim 1 in the form of a triple layered laminate containing sodium fluoride for anticaries protection having the following composition:

Ingredients	% w/w Bioadhesive Layer (0.1 mm)	Reservoir Layer (0.025 mm)	Outer Protective Barrier Membrane Layer (0.025 mm)
Polyethylene oxide homopolymer (MW 3,000,000 minimum)	60.0	-	-
Hydroxypropyl Cellulose (MW 1,000,000)	30.0	20.0	24.0
Polyethylene (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol (MW 400)	2.0	-	-
Ethyl Cellulose	-	59.0	69.6
Caprylic/Capric Triglyceride	-	5.0	6.0
Sodium Fluoride	-	16.0	0.4
	100.0	100.0	100.0

Patentansprüche

1. Ein pharmazeutisch verträglicher, dünner extrudierter Film, der ein Medikament enthält und kontrolliert freisetzt, mit einer einzigen oder mit mehreren Schichten, der die Fähigkeit aufweist, daß er auf der nassen Schleimhautoberfläche festkleben kann, umfassend eine wasserlösliche oder quellbare Polymermatrix einer bioadhäsiven Schicht, die auf der nassen Oberfläche der Schleimhaut kleben kann, wobei die bioadhäsive Schicht im wesentlichen aus 22,4 - 68,3 Gew.-% Hydroxypropyl-Cellulose mit einem Molekulargewicht von oberhalb 100 000, 23,75 - 60 Gew.-% eines Homopolymers von Ethylenoxid mit einem Molekulargewicht von oberhalb 100 000, 0 - 12,5 Gew.-% eines wasserunlöslichen Polymers, ausgewählt aus Ethyl-Cellulose, Propyl-Cellulose, Carboxymethyl-Cellulose in Form der freien Säure, Polyethylen und Polypropylen und 2,85 - 5 % eines Weichmachers besteht, wobei der Film eine pharmazeutisch wirksame Menge des Medikamentes inkorporiert enthält und das Medikament und die wahlweise enthaltenen Komponenten insgesamt 100 % ergeben.

2. Extrudierter Film nach Anspruch 1, der in einer Form hergestellt ist, die so dünn und flexibel ist, daß er, wenn er naß ist, den Patienten nicht stört, wenn er im Mund des Patienten an die richtige Stelle gelegt und eingebracht worden ist.

3. Extrudierter Film nach Anspruch 2 mit einer Dicke, die nicht größer als 0,25 mm ist.

4. Extrudierter Film nach Anspruch 3, bei dem die bioadhäsive Schicht des Homopolymers von Ethylenoxid ein Molekulargewicht von 3 000 000 bis 5 000 000 aufweist.

5. Extrudierter Film nach Anspruch 3 in einer mehrschichtigen laminierten Form, die zusätzlich zur bioadhäsiven Schicht noch eine Reservoir-Schicht enthält, in der zumindest ein Hauptanteil des Medikamentes enthalten ist.

6. Extrudierter mehrschichtiger Film nach Anspruch 5, in dem die Reservoir-Schicht im wesentlichen aus einer polymeren Matrix besteht, die sowohl aus einem wasserlöslichen und quellbaren Polymer und einem nichtwasserlöslichen Polymer besteht, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und auch Hydroxypropyl-Cellulose.

7. Extrudierter Film nach Anspruch 4 in Form eines mehrschichtigen Laminates, das zusätzlich zur bioadhäsiven Schicht auch eine äußere Schicht aus einer protektiven Membranbarriere enthält.

8. Extrudierter mehrschichtiger Film nach Anspruch 7, bei dem die äußere Schicht mit einer protektiven Membranbarriere dünner ist als die bioadhäsive Schicht und in dem die protektive Barriereschicht im wesentlichen aus einer Polymermatrix aus einem Hauptanteil eines nichtwasserlöslichen Polymers, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und einem geringeren Anteil von Hydroxypropyl-Cellulose, besteht.

9. Extrudierter mehrschichtiger Film nach Anspruch 1 in Form eines dreischichtigen Laminats, das Natriumfluorid zum Antikariesschutz enthält und das die folgende Zusammensetzung aufweist:

Bestandteile	bioadhäsive Schicht (0,1 mm)	% Gew./Gew. Reservoirschicht (0,025 mm)	äußere protektive Schicht der Membranbarriere (0,025 mm)
Homopolymer des Polyethylenoxids (MG mindestens 3 000 000)	60,0	-	-
Hydroxypropyl-Cellulose (MG 1 000 000)	30,0	20,0	24,0
Polyethylen (geringe Dichte)	5,0	-	-
Propylen-Glycol, U.S.P.	3,0	-	-
Polyethylen-Glycol (MG 400)	2,0	-	-
Ethyl-Cellulose	-	59,0	69,6
Capryl/Caprinsäure-Triglycerid	-	5,0	6,0
Natriumfluorid	-	16,0	0,4
	100,0	100,0	100,0

Revendications

1. Film mince extrudé mono- ou multicouche pharmaceutiquement acceptable contenant un médicament à libération contrôlée pouvant adhérer sur une surface de muqueuse humide, comprenant une couche bioadhésive de matrice de polymère gonflable ou soluble dans l'eau qui peut adhérer sur une surface de muqueuse humide et cette couche bioadhésive est constituée essentiellement de 22,4-68,3 % d'hydroxypropylcellulose ayant un poids moléculaire supérieur à 100 000, de 23,75-60% en poids d'un homopolymère d'oxyde d'éthylène ayant un poids moléculaire supérieur à 100 000, 0-12,5 % en poids d'un polymère insoluble dans l'eau choisi parmi l'éthylcellulose, la propylcellulose, la carboxyméthylcellulose exempte d'acide, le polyéthylène et le polypropylène, et 2,85-5 % d'un plastifiant, ledit film

contient une quantité pharmaceutiquement efficace du médicament qui y est incorporée, la présence du médicament et de composants éventuels faisant le complément du total de 100 %.

2. Film extrudé de la revendication 1, d'une forme suffisamment fine et souple quand il est humide de façon à ne pas gêner le patient quand il est placé et positionné correctement dans la bouche du patient.

3. Film extrudé de la revendication 2 ayant une épaisseur non supérieure à 0,25 millimètre.

4. Film extrudé de la revendication 3 dans lequel, dans la couche bioadhésive l'homopolymère d'oxyde d'éthylène a un poids moléculaire de 3 000 000 à 5 000 000.

5. Film extrudé de la revendication 3 sous forme feuilletée multicouche, qui contient aussi en plus de la couche bioadhésive une couche réservoir dans laquelle se trouve au moins une portion majeure du médicament.

6. Film multicouche extrudé de la revendication 5 dans lequel la couche réservoir est constituée essentiellement d'une matrice polymère contenant à la fois un polymère gonflable ou soluble dans l'eau et un polymère non soluble dans l'eau choisi parmi l'ethylcellulose, la propylcellulose, le polyéthylène et le polypropylène, et aussi de l'hydroxypropylcellulose.

7. Film extrudé de la revendication 4 sous forme feuilletée multicouche, qui contient en plus de la couche bioadhésive une couche membrane barrière de protection externe.

8. Film extrudé multicouche de la revendication 7 dans lequel la membrane barrière protectrice externe est plus mince que la couche bioadhésive, et ladite couche barrière protectrice externe est constituée essentiellement d'une matrice polymère composée en proportion majoritaire d'un polymère non soluble dans l'eau choisi dans le groupe de l'éthylcellulose, de la propylcellulose, du polyéthylène et du polypropylène, et d'une proportion mineure d'hydroxypropylcellulose.

9. Film multicouche extrudé de la revendication 1 sous forme d'un lamifié à triple couche contenant du fluorure de sodium pour la protection anticaries qui a la composition suivante :

Ingrédients	couche Bioadhésive 0,1 mm	% pds/pds Couche Réservoir (0,025 mm)	couche Membrane Barrière Protectrice Externe (0,025 mm)
Oxyde de Polyéthylène homopolymère (PM 3 000 000 minimum)	60,0	-	-
Hydroxypropylcellulose (PM 1 000 000)	30,0	20,0	24,0
Polyéthylène (basse densité)	5,0	-	-
Propylèneglycol, U.S.P.	3,0	-	-
Polyéthylèneglycol (PM 400)	2,0	-	-
Ethylcellulose	-	59,0	69,6
Triglycéride caprylique/caprique	-	5,0	6,0
Fluorure de sodium	-	16,0	0,4
	100,0	100,0	100,0